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Original Article

Radiotherapeutic Techniques for Prostate Cancer, Dose Escalation and Brachytherapy

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ABSTRACT:
There is evidence to confirm a dose–response relationship in prostate cancer. The relative benefit is dependent on the clinical prognostic risk factors (T stage, Gleason score and presenting prostate-specific antigen [PSA]) being more favourable for intermediate-risk patients. Refinement of prognostic groups and clinical threshold parameters is ongoing. Escalation of dose in prostate radiotherapy using conventional techniques is limited by rectal tolerance. Substantial advances have been made in radiotherapy practice, such as the development of conformal radiotherapy (CFRT) and intensity-modulated radiotherapy (IMRT). Randomised data support the value of CFRT in reducing rectal toxicity. IMRT can permit higher-dose escalation while still respecting known rectal tolerance thresholds. Brachytherapy is a recognised alternative for low-risk prostate cancer subgroups. New radiotherapeutic strategies for prostate cancer include pelvic nodal irradiation, exploiting the presumed low α/β ratio in prostate cancer for hypofractionation and combining external beam with high-dose-rate brachytherapy boosts. New image-guided methodologies will enhance the therapeutic ratio of any radiotherapy technique or dose escalation programme by enabling more reliable and accurate treatment delivery for improved patient outcomes. Khoo, V. S. (2005). *Clinical Oncology* **17,** 560–571
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Key words: Complications, conformal, dose escalation, hypofractionation, image-guided radiotherapy, intensity modulation, outcomes, prostate cancer, radiotherapy

Introduction

In the UK, the spectrum of men presenting with prostate cancer is changing from that of late stage or locally advanced cases to earlier stages of prostate cancer. This is largely a result of increased awareness of the disease and the liberal use of prostate-specific antigen (PSA) testing in general heath checks as well as 'de-facto' screening schemes. As a consequence, the incidence of prostate cancer is rising. From the Cancer Research UK website, prostate cancer is now considered the most common cancer in UK men, with an estimated 30 100 new cases annually [1]. It is anticipated that prostate cancer will affect one in every 14 men in the UK. It is highly likely that more patients will be considered for radical prostate radiotherapy in the near future.

The past two decades in radiation oncology has witnessed tremendous progress in new techniques for irradiation. Most of these developments have been initially trialled in the radiotherapeutic management of prostate cancer. This is because this disease subsite lends itself particularly well to new technology assessment. For localised disease, the prostate gland, with or without the seminal vesicles lying deep within the pelvis, is a relatively well-defined target. New radiotherapy techniques can be evaluated sooner in prostate cancer, as treatment outcomes can be assessed earlier by the use of surrogate tumour markers, such as PSA levels or prostate gland biopsies.

The overall steps inherent in the radiotherapeutic management of prostate cancer are shown in the radiotherapy treatment chain (Fig. 1). It is clear that each link in this chain is as important as each other and, in order to achieve optimal outcome clinically, due attention must be paid to each process within this chain. Substantial developments have been made for each of these links in this chain. The initial links of staging and determination of target volumes appropriate to the clinical scenario for prostate cancer radiotherapy is reviewed by Carey (Imaging for Prostate Cancer) within this issue, and will not be dealt with any further here.

This paper will deal with the progress in the planning, delivery and verification links of the treatment chain. It will discuss how these developments in radiotherapy techniques, including intensity-modulated radiotherapy (IMRT) and brachytherapy, have allowed changes in clinical

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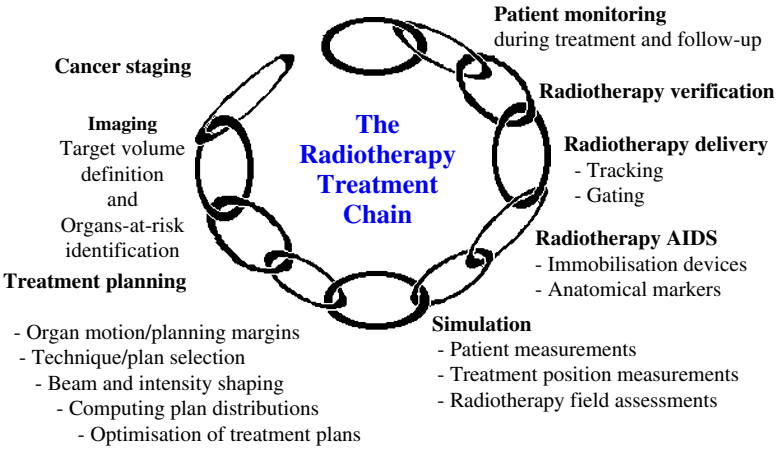

Fig. 1 – The radiotherapy treatment chain of the radiotherapeutic treatment process.

treatment strategies for prostate radiotherapy, such as escalation of radiation dose. It will also describe how these strategies may be potentially improved by recent advances in the understanding of prostate radiobiology and on-line radiotherapy imaging.

Traditional Prostate Radiotherapy and Treatment Outcomes

Traditionally, conventional external-beam radiotherapy for prostate cancer uses unshaped treatment fields designed from orthogonal radiographs and anatomical landmarks. Placement of treatment-field borders may be aided by the use of bladder-contrast media from a urinary catheter and rectal contrast. This two-dimensional method of treatment planning cannot accurately determine the internal position or shape of the prostate gland and its spatial relationship to surrounding normal organs, such as rectum and bladder. This uncertainty results in larger treatment volumes and excessive dose to the rectum or bladder.

Local prostate cancer control rates are related to clinical stage. It is best for T1-stage disease and drops with increasing T-stage. Using conventional external-beam prostate radiotherapy, the 10-year local tumour control rates are reported to range between 92% and 96% for T1 stage, 71% and 83% for T2 and 69% and 81% for T3 disease, and, at 15 years, it is 83% for T1, 65% and 68% for T2 and 44% and 75% for T3 stage [2–5]. It is important to note that these local control rates have been judged clinically, often using digital rectal examination, and pre-dates the routine use of PSA testing.

Rationale for Dose Escalation

Early data supporting a dose–response relationship in prostate radiotherapy was reported by the Patterns of Care group in the USA [6]. For local control of stage T0–T2 prostate cancer, doses of up to 60 Gy was reported to be adequate, but higher doses in the order of 65–70 Gy were needed for T3 disease and 70 Gy or more for T4 disease. Local control rates were increased from 62–63% using prescribed doses of less than 60 Gy to 74–80% for doses between 60 and 70 Gy and 81–88% when doses were greater than 70 Gy [7,8]. These data also relate principally to clinically detected cancers in assessments of local control.

In a study of 1127 men with prostate cancer treated with radiotherapy alone over a 10-year period (1987–1997), the dose prescribed was correlated to prognostic variables of pre-treatment PSA, Gleason score and T stage [9]. Three dose bands of 67 Gy or less, 68–77 Gy and greater than 77 Gy were determined. The actuarial 4-year freedom from biochemical PSA failure rates for the whole group was 54%, 71%, and 77% for each of the dose bands, respectively. On multivariate analysis, dose was noted to be an independent prognostic factor. Men with pre-treatment PSA of greater than 10 ng/ml benefited most from dose escalation. In men with PSA greater than 10 ng/ml and T1/2 stage disease, when the dose was increased from the intermediate-dose range to the high-dose range, the 4-year freedom from biochemical PSA failure rates increased from 61% to 93%. The higher-risk patients were not found to have benefited from dose escalation to the higher-dose range.

These data suggest that, for men with good prognostic features (PSA $\leq$10 ng/ml, T1/2 disease, Gleason summed score $<$7), radiation treatment alone with doses between 68 and 77 Gy seems to be adequate. Patients with intermediate prognostic features, where there is a raised value of one of the clinical prognosticators, such as PSA greater than 10 ng/ml, are likely to benefit from dose escalation. Patients with two or more raised values having poor prognostic features are at high risk and do not seem to benefit (substantially) from dose escalation. These patients may require additional therapy, such as androgen deprivation therapy or pelvic nodal irradiation.

Translation of improved local control rates into survival was reported for the first time by the Radiation Therapy

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